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POLYMERIC DIPHENYL METHYLENE DIISOCYANATE: 4-WEEK AEROSOL INHL TOX STUDY EVAL POTENTIAL TYPE II PNEUMOCYTE PROLIFERATION IN LUNGS OF MALE FISCHER 344 RATS W/CVR LTR DTD 05/24/94

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May 24, 1994

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Dear Sir or Madam:

In accordance with 40 CFR 716.30, the International Isocyanate Institute (III) on behalf of its members (BASF Corporation, Dow Chemical Company, ICI Americas, Inc., Miles, Inc., and Olin Corporation) hereby provides a copy of the following recently completed study report:

"Polymeric Diphenyl Methylene Diisocyanate: 4-Week Aerosol Inhalation Toxicity Study Evaluating Potential Type II Pneumocyte Proliferation in the Lungs of Male Fischer 344 Rats"

Name of Chemical Substances:	Polymeric Diphenyl Methane Diisocyanate
Chemical Abstract Service Number:	9016-87-9
Description of Study:	Inhalation exposure to respirable polymeric MDI aerosols
Date of Issue:	May 9, 1994
Name & Address of Testing Organization:	The Dow Chemical Company, The Toxicology Research Laboratory Health & Environmental Sciences

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Very truly yours,

R. K. Rigger
Managing Director

RKR/sha
Enclosure

Disposition of study file and summary:

Polymeric Diphenyl Methylene Diisocyanate: 4-Week Aerosol Inhalation Toxicity Study Evaluating Potential Type II Pneumocyte Proliferation in the Lungs of Male Fischer 344 Rats

Authors

B.L. Yano and T. D. Landry

Date

May 9, 1994

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Laboratory Project Study ID

TX-001160-008

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Polymeric Diphenyl Methylene Diisocyanate: 4-Week Aerosol Inhalation Toxicity Study Evaluating Potential Type II Pneumocyte Proliferation in the Lungs of Male Fischer 344 Rats

DISPOSITION OF STUDY FILE

The study will not be completed as originally planned because technical problems made generation of suitable MDI aerosol controlled test atmospheres very difficult. A probe study was conducted, but the 4-week study was not initiated. This summary is intended to provide an overview of the most important aspects of the work that was performed. It is not intended to provide details of the project. Because the study is not reported in entire detail, it is not intended to completely comply with GLP regulations. The study file is stored in the Dow Chemical Company's Health and Environmental Sciences archives.

A 4-day probe study was conducted at Dow's Toxicology Research Laboratory, but analyses of test atmosphere indicated that the MDI aerosol that had been generated was not suitable. Subsequent methodology development did not solve all the technical problems. Eighteen months after initiation, Dow study responsible persons and International Isocyanate Institute representatives decided to terminate the project. Although characterization of the lung inflam natory process following exposure to MDI aerosol might be helpful for evaluating the significance of the CIVO chronic inhalation toxicity study (Reuzel *et al.*, 1990), considerable resources were used in attempting to conduct this research project. A new technology (Proliferating Cell Nuclear Antigen, PCNA) appears to be emerging which in the future might allow evaluation of pulmonary cell reaction (mitoses) in a way more directly relateable to the CIVO chronic inhalation study.

SUMMARY

METHODS

Groups of five male Fischer 344 rats were exposed to targeted concentrations of 0, 0.2, 6.0, or 15 mg MDI/m^3 for four days. Rats were weighed on days 1 and 4. On the day after the fourth exposure, fasted rats were anesthetized with methoxyflurane, each diaphragm was punctured following

an abdominal incision, and the rats were exsanguinated. The tracheas were exposed, clamped, cannulated and infused with ice-cold acetone at a pressure of approximately 20 - 25 cm of fixative and a flow rate of approximately 100 - 130 ml/min. The tracheas were ligated at the level of the cannula, and the lungs were removed. Lungs were placed in cold fixative for another two to three hours. Mediastinal tissues, heart, and the trachea were trimmed from the lungs and the lung volumes were determined. The nasal turbinates were flushed with neutral-phosphate-buffered 10% formalin. The nasal turbinates and the larynx were placed in the same fixative. The nasal turbinates, larynx, trachea, lung and duodenum were prepared for histologic evaluation. The nasal turbinates, larynx and trachea were prepared by standard techniques and stained with hematoxylin and eosin. The lungs and duodenum were immunohistochemically stained for BrdU and the same section of lung was also stained to detect alkaline phosphatase activity.

The Dow probe study was conducted using a condensation aerosol of technical grade MDI (Desmodur 44 V 20 supplied by Bayer AG, Leverkusen, Germany) containing 51% MDI monomer. Preliminary evaluations of test atmospheres indicated that the aerodynamic size of particles in the 0.2 and 15 mg/m^3 chambers was adequate (2.9 and 4.5 μ, respectively) to "administer" particles to the lung. During the four-day probe study, while rats were in the chambers, the particle size distributions significantly differed between exposure groups (Text Table 1). Particles above 4 to 5 μ in

Exposure Group	Chamber conc. (mg/m^3 +/-SD)	MMAD (μ +/- SD)
0 mg/m^3 (control)	0.0 +/- 0.0	---
0.2 mg/m^3	0.2 +/- 0.0	14.1 μ +/- 3.2
6 mg/m^3	3.5 +/- 1.7	5.1 μ +/- 2.0
15 mg/m^3	17.5 +/- 1.7	5.5 μ +/- 1.9

Text Table 1 MDI aerosol exposure conditions during Dow's 4-day probe study.

diameter have a relatively lower probability of deposition in the lung. The particle size distribution was marginally adequate to assess pulmonary effects in the 6 and 15 mg/m^3 groups, but inadequate in the 0.2 mg/m^3 group. Data would not be comparable between groups with such markedly different particle size distributions.

RESULTS - SUMMARIZED

Some biological information was obtained during the probe study before the analytical results were fully evaluated. Rats appeared normal based on routine daily observations. Exposure to 6 or 15 mg/m^3 resulted in reduced body weight gain from day 1 to day 4 (Text Table 2).

Exposure Group	Mean Body Weight (g) +/- SD	
	Day 1	Day 4
0 mg/m^3 (control)	219 +/- 9	223 +/- 8
0.2 mg/m^3	213 +/- 7	219 +/- 8
6 mg/m^3	219 +/- 7	208* +/- 10
15 mg/m^3	217 +/- 6	174** +/- 5

Statistically different from control value by Dunnett's at $p<0.05$ (*) or $p<0.01$(**).

Text Table 2 Body weight summary for male rats exposed to MDI aerosol (n=5 rats/group).

A very slight increase in mucous and/or mucous cells was histologically observed in the anterior portion of the nasal turbinates of the majority of the rats exposed to either 6 or 15 mg/m^3 (Table 1). Very slight inflammation and/or squamous metaplasia also occurred in the larynx and trachea of one or two rats exposed to 15 mg/m^3. A very slight increase in the numbers of BrdU and alkaline phosphatase positive cells was noted in the bronchi and bronchioles of all rats exposed to 15 mg/m^3 and in 2 of 5 rats exposed to 6 mg/m^3. These positively staining cells were consistent with Clara cells. The duodenum of all rats stained positive for BrdU and alkaline phosphatase, indicating that the staining procedures used were adequate for the intended use.

DISCUSSION

These results are generally consistent with the CIVO studies of MDI sub-acute toxicity as reported by Reuzel (1983). At CIVO, exposure-related effects were established for clinical signs, body weight gain and lung/body weight ratio. These effects were marked in rats exposed to 15 mg/m^3 (where deaths occurred), and were less marked at 5 mg/m^3. Only the lung/body weight ratio was affected at 2 mg/m^3. Precise comparisons are not being made between the Dow probe study and the CIVO study, though the similarity provides some perspective on the comparability of the finding of respiratory tract irritation.

Methodology Work After the Probe Study

Work was continued to develop suitable exposure methods. A Schlick model 970 spray nozzle (Orthos Inc., Schaumburg, IL) generated a concentration of 15 mg/m^3 over a period of 3+ hours based on gravimetric analysis, the MMAD was between 1 and 3 μ at 15 mg/m^3. MDI specific analysis and gravimetric analysis were consistent at chamber concentrations of 15, 80, and 130 mg/m^3. A TSI APS 33 laser velocimeter (TSI, Inc., St. Paul, MN) was tested and appeared to provide rapid indication of chamber concentration. Although these aerosol generation & analysis procedures were not tested at the range of concentrations that would be required in a toxicology study, this procedure might be a useful starting point if further aerosol inhalation studies were to be performed.

References

Reuzel, P.G.J. (1983). Preliminary studies of polymeric MDI aerosols and a sub-acute (2-week) inhalation toxicity study of polymeric MDI in rats. CIVO report # 83.321/212478 (III - 10119).

Reuzel, P.G.J., Arts, J.H.E., Kuypers, M.H.M. and Kuper, C.F. (19[illegible]). Chronic toxicity/carcinogenicity study of polymeric MDI aerosol in rats. Final report. CIVO report # V88.122 (III - 10749).

MDI: 4-Day Probe Study

TX-001160-008

Table 1: Histopathology - Summary

Conc. (mg/cu m)	0	0.2	6	15
Number of Rats	5	5	5	5
Nasal Turbinates				
Within normal limits	4	5	1	0
Inflammation- subacute to chronic, Level 4, very slight	1	0	0	0
Increased mucous/mucous celis, Level 1, very slight	0	0	4	5
Larynx				
Within normal limits	5	5	5	4
Inflammation-subacute to chronic,very slight	0	0	0	1
Trachea				
Within normal limits	0	0	0	3
Squamous metaplasia, very slight	0	0	0	1
Inflammation-subacute to chronic,very slight	0	0	0	1
Lung				
Within normal limits	5	5	3	0
Increased BrdU in AP (+) cells, bronchi/bronchioles, very slight	0	0	2	5
Duodenum				
Within normal limits	5	5	5	5
Positive BrdU and AP staining	5	5	5	5

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